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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,209	09/28/2005	Denise M. Baker	2473.0260001/EKS/PAC	8322

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EXAMINER
DIBRINO, MARIANNE NMN

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
12/21/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,209	BAKER ET AL.	
	Examiner	Art Unit	
	MARIANNE DIBRINO	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/24/10*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,16,2326, 31 and 31-44* is/are pending in the application.

4a) Of the above claim(s) *3-7,23,26 and 33-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,16 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and response filed 9/24/10 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election with traverse of species of (i) identifying from a particular antigen of a particular infectious agent variants of a class I MHC peptide epitope 8-11 amino acid residues in length, each variant comprising primary anchor residues of the same HLA class I binding motif, determining whether each of said variants comprises conserved, semi-conserved or non-conserved non-anchor residues in comparison to each of the remaining variants, and identifying a variant which comprises only conserved non-anchor residues in comparison to at least one remaining variant, in the response filed 6/11/09.

Claims 1, 2, 16 and 32 are currently being examined.

3. Applicant's amendment filed 9/24/10 has overcome the prior rejection of claims 1, 2, 16 and 32 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

4. Upon reconsideration, the prior rejection of record of claims 1, 2, 16 and 32 under 35 U.S.C. 102(a) as being anticipated by De Groot *et al* (Immunology and Cell Biology, 2002, 80: 255-269, of record) has been withdrawn.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claim 1 is indefinite in the recitation of "from the same, and" at part "b)" because it is not clear what is meant.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1, 2, 16 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over De Groot *et al* (Immunology and Cell Biology, 2002, 80: 255-269, of record) in view

of Paul (Fund. Immunol. 5th Edition, Lippincott Williams & Wilkins, Philadelphia, pages 666-667, 2003, of record).

Applicant has amended base claim 1 to recite testing the candidate peptide epitope for the ability to induce a HLA class I CTL response against at least one variant of the peptide epitope.

De Groot *et al* teach comparing the sequence of 8-11-mer peptides across strains of infectious agents such as HIV-1 to identify broadly conserved (cross-clade) epitopes (that contain motifs for binding a particular MHC class I molecule, that is, anchor residues, both primary and secondary), and further teach including in the method, the allowance of amino acid substitutions at non-anchor positions. The art reference teaches that the degree of intra- and –inter-clade cross-reactivity will be determined by factors that include the degree of sequence conservation of CTL epitopes, *i.e.,* the degree of sequence conservation at all positions in the peptide. De Groot *et al* teach testing the peptides for binding to class I MHC and teach the importance of testing the immunogenicity of an HLA binding peptide in HLA transgenic mice and/or in a *in vitro* assay for CTL reactivity (see entire reference).

In greater detail, De Groot *et al* teach using Conservatrix to determine peptide subsequences across-clades for a particular protein, in the instant case, an HIV protein, configuring the program to allow amino acid substitution at non-anchor positions and identifying highly conserved peptides across-clades. In addition, De Groot *et al* teach use of EpiMatrix, which evaluates the contribution of each amino acid residue in the peptide for potential to bind to a particular MHC class I molecule (*i.e.,* it provides the teaching that each amino acid residue in the peptide can influence binding (independent side chain contribution, especially page 260 at column 2, lines 1-3 and paragraph 2).

De Groot *et al* do not teach determining whether one of the variant peptides has only conservative substitutions at non-anchor positions.

Paul teaches that T cell receptors (TCRs) may distinguish different chemical classes of amino acid side chains. Paul teach that an example of structural differences between amino acid side chains recognized by the TCR comes from an analysis of non-cross reactive CTLs that distinguish homologous peptides from the V3 loop of different strains of HIV-1 envelope protein. Paul teaches that the two non-cross reactive TCRs recognize similar peptides but discriminate strongly between peptides with amino acids with aliphatic versus aromatic side chains, but on the other hand they do not distinguish strongly amongst different aliphatic residues or among different aromatic residues. Paul teaches that valine, leucine or isoleucine (conservative substituents) at a key TCR contact residue (position 8 of the peptide sequence) can be recognized by the same TCR, while non-conservative substituent tyrosine can not and visa versa (paragraph spanning pages 666-667 and first full paragraph at column 1 on page 667).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have selected for conservative substitutions at non-anchor residues.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because first of all, those residues may serve as T cell contact residues and one of ordinary skill in the art was aware, as illustrated by Paul, that TCR have a degree of fine specificity but may be permissive of conservative substituents in the peptide, and second of all, the De Groot *et al* teach that all the amino acid residues in a peptide may promote or interfere with binding to MHC and that sequence conservation is important for CTL-reactive peptide epitopes within and across HIV-1 clades.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have tested the candidate peptide epitope for the ability to induce an HLA class I response against at least on variant of the peptide epitope.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because De Groot *et al* teach the importance of intra-and inter-clade cross-reactivity of the peptides in vaccine design and also teach the importance of testing the immunogenicity of an HLA binding peptide in HLA transgenic mice and/or in a *in vitro* assay for CTL reactivity.

Applicant's arguments have been fully considered but are not persuasive.

Applicant's said arguments are of record on pages 13-16 of the amendment filed 9/24/10.

However, it would have been prima facie obvious to have selected a peptide with only conserved non-anchor amino acid residues whether or not they are TCR contact residues. De Groot *et al* teach using Conservatrix to determine peptide subsequences across-clades for a particular protein, in the instant case, an HIV protein, configuring the program to allow amino acid substitution at non-anchor positions and identifying highly conserved peptides across-clades. In addition, De Groot *et al* teach use of EpiMatrix, which evaluates the contribution of each amino acid residue in the peptide for potential to bind to a particular MHC class I molecule (*i.e.,* it provides the teaching that each amino acid residue in the peptide can influence binding (independent side chain contribution, especially page 260 at column 2, lines 1-3 and paragraph 2). De Groot *et al* recognize the importance of selecting peptides that provide broad coverage. De Groot *et al* teach that the degree of intra- and –inter-clade cross-reactivity will be determined by factors that include the degree of sequence conservation of CTL epitopes, *i.e.,* the degree of sequence conservation at all positions in the peptide, *meaning conservative substitutions*. It would have been obvious to select a peptide that could bind to a same MHC class I molecule that has only conserved non-anchor

residues in comparison with at least one other peptide from another clade because that peptide would be expected to be cross-reactive.

Note that the art reference method teaches that the non-anchor positions are assessed for conserved, semi-conserved or non-conserved amino acid residues because knowledge of what is a conserved amino acid residue is necessarily also a comparison with what is not a conserved amino acid residue.

Applicant asserts that the cross-reactivity of the resulting variant in inducing broad immune responses is an unexpected and superior property disclosed in De Groot. Applicant cites at least Example 2 of the instant specification to support this assertion.

However, Applicant is arguing the references separately. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In addition, in Example 2 of the specification, peptide variants are assessed for various anchor and non-anchor positions, for binding to class I MHC and changes in recognition by CTL. Likewise, the art teaches assessing these parameters. In addition, Example 2 discloses identifying variant peptides by using supertype motifs, an unrecited limitation, and further discloses that choice of the variant peptide as the most common within a clade *vs* in all clades influences the degree of cross-reactivity with other variant peptides, another unrecited limitation.

8. No claim is allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-

0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ram Shukla, can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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